REMARKS

Claims 10, 16-24, and 33-38 are pending and under consideration in the present application. Claims 1-9, 16-18, 20, 24-32, and 34-36 have been canceled herein without prejudice. Claims 10, 19, 21, 33, 37, and 38 have been amended herein. Claims 39-42 have been newly added. Upon entry of the present amendment, claims 10, 19, 21-23, 33, and 37-42 will be pending and under consideration.

No new matter is added by the present amendments and added claims. The amendments to claims 10, 19, and 33 clarify that the detection methods include a determination of the methylation state of at least one of a first region or a second region, which are the regions of the CACNA1G CpG island that are amplified by SEQ ID NO:33 and SEQ ID NO:34 or by SEQ ID NO:35 and SEQ ID NO:36, respectively. These amendments are supported, for example, by claim 16 as originally filed, and Table 3 on page 37, which indicates that the primer pair SEQ ID NO:33 and SEQ ID NO:34 and the primer pair SEQ ID NO:35 and SEQ ID NO:36 are primer pairs for amplifying Region 1, and Region 2 of the CpG island of CACNA1G, respectively. These amendments, as well as the amendment to the preamble of claims 10 and 33, which recite that the claims are directed at methods for detecting colorectal adenoma or a cancer other than glioma, are also supported, for example, by page 25, lines 16-19, and page 28, lines 16-17 which indicate that regions 1 and 2 of the CACNA1G CpG island were methylated in most cancer cell types except gliomas. Furthermore, the amendment to the preamble is supported by claim 24, as originally filed, and page 30, lines 18-26, which lists examples of cell proliferative disorders.

The amendment to claim 21 cancels primer pairs that are not directed at the first or second region of the CACNA1G CpG island. Claims 37 and 38 are amended herein to delete terms to remain consistent with claim 33, from which they depend. Newly added claim 39 is supported, for example, by page 27, lines 15-20. Newly added claims 40-42 are supported, for

example, by claim 17 as filed, which recites that hypermethylation of regions 5-7 can be analyzed to detect a cellular proliferative disorder, and Tables 2 and 3, which provide the SEQ ID NOS: of primer pairs for amplifying the recited regions of the CACNA1G CpG island. Furthermore, newly added claims 40-42 are supported by page 26, lines 2-3, which indicate that the 5' region of CACNA1G is the downstream CpG island (regions 5-7), Table 3 on page 37, which provides the SEQ ID NOS for the primer pairs used to amplify regions 5-7, and page 27, lines 15-25, which indicates that the 5' region of CACNA1G (i.e., regions 5-7) are aberrantly methylated in colorectal cancers, colorectal adenomas, gastric cancers, and AML.

Rejection Under 35 U.S.C. § 112, Enablement

Claims 10, 16-24, and 33-38 stand rejected under 35 U.S.C. § 112, first paragraph, as allegedly not being disclosed in the specification in such a way as to enable one skilled in the art to make and/or use the invention. Applicant respectfully traverses the rejection. The Office Action mailed November 13, 2002 reiterates verbatim the allegation of the previous Office Action that the present invention is not enabled because the claimed invention is overly broad in being directed to identifying any cellular proliferative disorder, and to any CpG island within the recited genes. Furthermore, the Office Action of November 13, 2002 repeats verbatim the assertion in the previous Office Action that it is unpredictable which CpG islands, and which subregions within those islands, are associated with various tissues based on cited published reports (e.g., Toyota et al., *Blood*, Vol. 97, 2823 (2001)), and results of the present specification, which indicate that the hypermethylated gene CACNA1G, is not hypermethylated in all cell proliferative disorders. Finally, the Office Action reasserts its allegation that the present invention is not enabled because experimental details are not presented regarding the correlation

of hypermethylation and cellular proliferative disorders for all of the recited genes, except CACNA1G.

In response to the Applicant's arguments in the Response filed August 15, 2002, the Office Action cites Moinova et al. (*PNAS*, 99:4562, 2002) to allegedly establish that genes that are hypermethylated in certain cancers are not hypermethylated in all cancers, as allegedly exemplified by hypermethylation of the HLTF gene in primary colon cancer, but not breast or lung cancer. Furthermore, the Office Action cites Kazuhiro et al. (*Clin. Cancer Research*, 8: 3164) in allegedly teaching that MLH1, HRK and CACNA1G are not methylated in oral squamous cell carcinomas. As a preliminary matter, "Kazuhiro et al." cited in the Office Action is cited herein as Ogi et. al. (*Clin. Cancer Research*, 8, 3164 (2002)).

A close comparison of Ogi et al. with the pending application further establishes that the CpG island of CACNA1, as defined in the present specification, is hypermethylated in the vast majority of cancers. Ogi et al. analyze methylation of 12 loci in squamous cell carcinomas (SCC), including CACNA1G and MINT31. Although they report that CACNA1G did not exhibit aberrant methylation, they report that MINT31 exhibited aberrant methylation. The specification of the present application indicates that the CACNA1G CpG island is divided into 8 regions. Regions 1 and 2 of the CACNA1G CpG island, the regions amplified by SEQ ID NOS:33 and 34 and SEQ ID NOS:35 and 36, respectively, correspond to a region in and around MINT31 (Page 26, lines 1-2; Page 27, lines 27-29; and Figure 1b). Therefore, Ogi et al.'s report of hypermethylation of MINT31 in SCC, is consistent with the present specification's disclosure of hypermethylation of regions 1 and 2 of CACNA1G in a variety of cancers. In fact, the present specification indicates that "[t]he CpG island around MINT31 is much more frequently methylated in cancers compared to that just upstream of CACNA1G" (Page 28, lines 16-17).

As indicated in the present specification, regions 1 and 2, the regions in and around MINT31, were frequently methylated in cancer cell lines (See e.g., Page 28, lines 16-17). The present specification provides details regarding the specific patterns of methylation within the CpG region of CACNA1G. The specific patterns observed illustrate that methylation of regions 1 and 2 (island 1) is frequent in cancers, since methylation of these regions is included in all of the methylation patterns of the CANA1G methylation. Furthermore, the present specification teaches that regions 1 and 2 of the CANCA1G CpG region are much more frequently methylated in cancers compared to the CpG island just upstream of CACNA1G (Page 28, lines 16-17).

The Office Action further alleges that not all subregions of CACNA1G are hypermethylated in all cancers, for example gliomas. Claims 10 and 33 as amended recite that the claimed method is not directed at detecting gliomas. Additionally, the present specification discloses that regions 1 and 2 of the CACNA1G CpG island, which are in and around MINT31, are hypermethylated in a wide variety of cancers (See e.g., page 25, lines 16-18). Furthermore, the specification discloses that regions 1 and 2 of the CACNA1G CpG island are hypermethylated in primary cells and cell lines from colon cancer, lung cancer, hematopoietic cancer, prostate cancer, and breast cancer (See e.g., page 24, line 24 to page 25, line 18).

Reports published after the priority date of the pending specification, further establish that the entire MINT31 sequence and regions 1 and 2 of the CACNA1G CpG island, as defined in the present specification, are hypermethylated in a wide variety of cancers. For example, Toyota et al., teach that regions 1 and 2 of the CpG island of CACNA1G are hypermethylated in cancer cell lines from colon, lung, prostate, breast, brain, and hematopoietic neoplasms (*Cancer Research* 59:4535, at Fig. 2 (1999)). As indicated above, Ogi et al., establish that MINT31 is hypermethylated in oral squamous cell carcinoma. Furthermore, the Office Action acknowledges regarding Toyota et al, that the presence of hypermethylation of CACNA1G in some AML

patients is commensurate in scope with the claims (Office Action at page 10) (*Blood*, 97:2823 (2001)). In addition, Chan, A.O., et al., (*Amer. Journ. Path.*, 160:529 (2002)(see e.g., Abstract)), and Rashid, A., et al., (*Amer. Journ. Path.*, 159:1129 (2001)), report that methylation of MINT31 is a common feature of the CpG island methylator phenotype (CIMP) of colorectal carcinomas and adenomas. Finally, Strathdee et al report that MINT31 is frequently methylated in primary ovarian carcinomas (*Amer. Journ. Path..*, 158:1121 (See e.g., Table 1)).

The Advisory Action mailed April 7, 2003 asserts that the amendment to claim 33 that recites "colorectal adenoma or a cancer other than glioma" would require further consideration. As indicated above, these claims are supported by the disclosure as filed. For example, page 25, lines 16-19 and page 28, lines 16-17 indicate that regions 1 and 2 of the CACNA1G CpG island are methylated in most cancer cell types except gliomas.

Furthermore, the Advisory Action alleges regarding the first region and second region of the CACNA1G CpG island, that it is unclear whether these regions are those set forth in the specification as regions 1 and 2, and unclear as to whether these regions correspond to SEQ ID NOS:35 and 36, and/or MINT31. Claims 10 and 33 as amended clarify that the methods include a determination of the methylation state of at least one of a first region or a second region, which are the regions of the CACNA1G CpG island that are amplified by SEQ ID NO:33 and SEQ ID NO:34 or by SEQ ID NO:35 and SEQ ID NO:36, respectively. Furthermore, the specification of the pending application clarifies the relationship between regions 1 and 2 of the CACNA1G island, and MINT 31. Regions 1 and 2 of the CACNA1G CpG island, the regions amplified by SEQ ID NOS:33 and 34 and SEQ ID NOS:35 and 36, respectively, correspond to regions in and around MINT31 (Page 26, lines 1-2; Page 27, lines 27-29; and Figure 1b).

In summary, the claimed inventions of the pending claims are enabled by the disclosure as filed. Therefore, Applicant respectfully request withdrawal of the rejection of claims 10, 16-24, and 33-38 under 35 U.S.C. § 112, first paragraph.

In view of the amendments and the above remarks, it is submitted that the application is in condition for allowance and a notice to that effect is respectfully requested. The Examiner is invited to contact Applicants' undersigned representative if there are any questions relating to this application.

Please charge any additional fees, or make any credits, to Deposit Account No. 50-1355.

Respectfully submitted,

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